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## The heritability of risk and age at onset of Parkinson's disease after accounting for known genetic risk factors

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### Abstract

We questioned if the evidence for the genetic component in PD in Caucasians could be explained by the causative and susceptibility genes that have already been identified. We estimated heritability of risk and age at onset of PD in a well-characterized sample of 504 nuclear families (2,828 individuals). After excluding families with known pathogenic mutations and accounting for the major susceptibility genes, the heritability of the risk of developing PD was 0.41 ( $P=0.01$ ). These data suggest approximately 40% of the variation in susceptibility to PD is due to as yet unidentified genes, the remainder is likely environmental.

### Keywords

Parkinson's disease; heritability; age at onset; risk; gene; environment

### Introduction

Family studies conducted in Caucasian populations suggest Parkinson's disease (PD) has a strong genetic component,<sup>1–5</sup> yet genome-wide association studies (GWAS) have not uncovered any new genes that reached the statistically acceptable significance level.<sup>6–9</sup> The greatest hits have been in and around the alpha-synuclein (*SNCA*) and tau (*MAPT*) genes, which were already known and firmly established as risk factors for PD.<sup>10–12</sup> In contrast, a GWAS conducted in the Japanese population identified two novel PD-associated loci.<sup>13</sup> We questioned whether the bulk of evidence for a genetic component in PD in the Caucasian population was due to the genes that have since been discovered.

### Methods

The study was approved by the Institutional Review Board Human Subject Committee. We used a dataset of 504 nuclear families with 2,828 individuals to estimate heritability of PD (Table 1). The families were parents and siblings of 504 Caucasian probands with a UK Brain Bank diagnosis of PD.<sup>14</sup> The probands were ascertained irrespective of age at onset or family history from a single NeuroGenetics Research Consortium (NGRC) movement disorder clinic in Portland, Oregon. We selected this subset of NGRC dataset because we had detailed, uniform, systematically collected and verified family history data on them.<sup>2</sup>

Probands were genotyped for the following known causative and susceptibility PD genes: *SNCA* point mutation and multiplication, *PRKN* point mutation and deletions and multiplications, *LRRK2* G2019S and R1441 mutations, *Nurr1* mutations, *DJI* mutations

(genotyped in familial and early-onset PD only), *SCA2* triplet repeat expansion (familial PD only), *MAPT* H1/H2 diplotype, and *SNCA* REP1, 5' and 3' polymorphisms. We did not have genotypes for *PINK1* and *GBA*; the mutations in these genes are rare and would not alter the results. Available family members were genotyped if the proband had a pathogenic mutation. Family members were not genotyped for susceptibility loci. This did not affect heritability of risk. In the analysis of age at onset, family members were conservatively assigned the genotype of the probands, which might have inflated the heritability attributed to *SNCA* and *MAPT*, and underestimated the heritability due to unknown genes.

We estimated heritability for two phenotypes: risk of developing PD, and age at onset of PD. Each phenotype was tested three times. First, we used the entire sample of 504 families. Next, we limited the sample to subjects who had no known pathogenic mutation (excluded 10 families whose probands had one *LRRK2*, *SNCA*, or *SCA2* mutation or two *PRKN* mutations). Finally, we excluded the pathogenic mutations and accounted for susceptibility genotypes by adjusting for (age at onset analysis) or excluding (risk analysis) probands who had *MAPT* H1H1 diplotype or *SNCA* high risk genotype. For *SNCA*, we used a single nucleotide polymorphisms in the 3' region of the gene (rs356220) which gives the strongest signal for association of *SNCA* with PD in our dataset ( $p=10^{-11}$ ). We also analyzed the data using *SNCA* REP1 and results were similar. Narrow-sense heritability ( $h^2$ ), defined as the proportion of the total phenotypic variance explained by additive genetic effects, was calculated using maximum likelihood variance components analysis in SOLAR version 4.2.0 software package,<sup>15</sup> setting PD prevalence at 1% and adjusting for gender. We did not adjust for age because unaffected family members were nearly a decade past the age at onset of their affected relatives.

## Results

Heritability estimates are shown in Table 2. Heritability of risk for the entire sample before exclusions was 0.60 ( $P<0.0001$ ), which is similar to a prior study of heritability of PD risk.<sup>16</sup> Excluding the pathogenic mutations reduced the estimate only slightly (0.58,  $P<0.0001$ ) because pathogenic mutations occurred in only 2% of the study population. Excluding all families whose proband had a pathogenic mutation or a high risk *SNCA* or *MAPT* genotype further reduced heritability, but only to 0.41 ( $P=0.014$ ). These data suggest that (a) there remains a significant and substantial genetic component to the risk of developing common idiopathic PD after accounting for the known genes and (b) these putative genes explain only about 40% of the variability in PD susceptibility; the remaining variability is likely environmental.

Heritability of risk described above was estimated for the entire clinic population, which was ascertained regardless of family history or age at onset and therefore was more representative of common idiopathic PD than the sample that will be presented next for estimating heritability of age at onset. Estimating heritability of age at onset requires data from families that have at least two affected members, which by definition is familial PD.

There has been no published heritability study of age at onset of PD to date. In our study, affected siblings exhibited high correlation in age at onset ( $r=0.74$ ,  $P<0.001$ ). Heritability of age at onset in the siblings before exclusions was 0.98 ( $P=0.0002$ ). This unusually high estimate is in line with complex segregation analyses, which have consistently suggested stronger genetic influence on onset age than on risk of PD.<sup>17, 18</sup> Also note that the sample consists of affected siblings, which is enriched in familial, including autosomal recessive, PD. Heritability dropped to 0.76 ( $P=0.015$ ) after excluding pathogenic mutation carriers, and to 0.22 ( $P=0.3$ ) after excluding mutation carriers and adjusting for *SNCA* and *MAPT*.

There was no correlation in age at onset of parents and offspring ( $r=0.09$ ,  $P=0.54$ ). Age at onset was on average 10 years earlier in the offspring generation than in parents (Table 1), which is consistent with genetic anticipation, or recessive inherited disease in offspring and sporadic late-onset disease in parents. Although results would be difficult to interpret, for completeness, we estimated heritability of onset age using all affected parents and siblings: 0.51 ( $P=0.001$ ) for all families, 0.28 ( $P=0.088$ ) after excluding pathogenic mutation carriers, and zero after excluding mutation carriers and adjusting for susceptibility genotypes.

## Discussion

Our data suggest that the genes identified to date explain a notable portion of the heritability of age at onset in familial PD, but they account for only a modest portion of genetic contribution to the risk of developing common, idiopathic PD. We conclude that there exist as-yet unidentified PD susceptibility genes that account for about 40% of the variation in PD risk. If there are genes to be found, why have they eluded GWAS? Despite their increasing sample sizes, none of the GWAS to date has had the analytical power to detect genes with small effects. Collaborative Meta-analyses can help overcome the sample size limitation. If the genetic variants relevant to PD are rare, they would be missed by current genotyping arrays. To find rare alleles, whole genome sequencing may be necessary, which is not yet a reality but is on the horizon. Another possibility is that susceptibility genes do not have a detectable effect in isolation from the environmental factors with which they interact. PD has long been suspected to result from interplay of genetic susceptibility to environmental toxins, and data in support of this notion is beginning to emerge.<sup>19</sup> Data presented here also suggests genes and environment are equally important in susceptibility to PD. It will be interesting to see if Meta-analyses and gene-environment interaction studies will identify additional PD susceptibility genes in Caucasians.

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**Table 1**

Characteristics of the probands and their first degree relatives

Subjects	N	Affected with PD		Unaffected	
		% male	Mean onset age $\pm$ SD	% male	Mean age $\pm$ SD
Probands	504	60.71	57.89 $\pm$ 11.77	-	-
Siblings of probands	32	59.38	55.79 $\pm$ 18.46	1284	51.29
Parents of probands	56	48.21	65.65 $\pm$ 12.80	948	50.00
					75.74 $\pm$ 14.95

**Table 2**

## Heritability of Parkinson's Disease

	N families	h <sup>2</sup>	se	P
<b>Heritability of Risk in unselected clinic patients</b>				
All families	504	0.60	0.10	<.0001
Mutation carriers excluded	494	0.58	0.06	<.0001
Mutation carriers & high risk at SNCA 3' and MAPT excluded	105	0.41	0.10	0.014
<b>Heritability of onset age in familial PD</b>				
All sib pairs	28	0.98	0.25	0.0002
Mutation carriers excluded	25	0.76	0.32	0.015
Mutation carriers excluded & adjusted for SNCA 3' and MAPT	19	0.22	0.47	0.323